Complete Summary

GUIDELINE TITLE

Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours. London (UK): National Institute for Clinical Excellence (NICE); 2004 Oct. 38 p. (Technology appraisal; no. 86).

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Unresectable and/or metastatic gastro-intestinal stromal tumours (GISTs)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Internal Medicine
Oncology

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To assess the clinical and cost-effectiveness of imatinib in the treatment of unresectable and/or metastatic, KIT positive, gastrointestinal stromal tumours (GISTs), relative to current standard treatments

TARGET POPULATION

Patients with unresectable and/or metastatic gastro-intestinal stromal tumours

INTERVENTIONS AND PRACTICES CONSIDERED

Imatinib

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness: The following outcomes were considered whenever available: Quality of life (most preferred), mortality (overall survival and median survival times), morbidity, and tumour response. (Tumour response could be measured using computed tomography [CT] scans, magnetic resonance imaging [MRI] scans, or positron emission tomography [PET] scans).
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the West Midlands Health Technology Assessment Collaboration (see the "Companion Documents" field).

Search Strategy

The search strategy was divided into 6 parts and aimed to look for trials of imatinib (with or without standard treatment comparators), trials of alternative/experimental treatments, studies that had observed patient prognosis without treatment (to enable a comparison of disease progression should trials without comparators be available), and diagnostic papers in order to gain an insight into the uncertainty of gastro-intestinal stromal tumour (GIST) diagnosis and possible consequences of treating false positives. In addition ongoing trials were sought, as imatinib is a very recent drug. A search for economic evaluation of treatments for GIST was also conducted.

The searches were not restricted by language. Published and unpublished studies were sought. Databases were searched from inception. Searches (except for ongoing trials) were undertaken between 25 April and 15 May 2003.

See the section 2 of the assessment report for details of the electronic search.

Inclusion and Exclusion Criteria

A three stage sorting process was instigated to look through the yield of the search.

Stage 1 - Including or Excluding Studies

Two reviewers independently assessed papers for inclusion/exclusion using the title and where available the abstract. The following inclusion criteria were applied:

Inclusion Criteria

Study design: Relevant randomised controlled trials (RCTs), non-randomised controlled studies, cohort studies, and case series that reported effectiveness results of treatment with imatinib and/or other interventions in patients with GIST.

Population: Ideally patients diagnosed cKIT positive unresectable and/or metastatic GISTs (including primary or recurrent tumours). Not so ideal but still included were patients histologically diagnosed with GIST. In trials older than 1999 patients who were diagnosed with gastrointestinal leiomyosarcoma or soft tissue sarcoma that appeared to behave as GIST (e.g., tendency to metastasize in the liver), were included. Early terms for GIST4 could include oesophageal leiomyosarcoma; gastric leiomyoma; gastric leiomyoblastoma; small intestinal leiomyoma and leiomyosarcoma; colonic and rectal leiomyoma and leiomyosarcoma; gastrointestinal autonomic nerve tumour (GANT); leiomyoma and leiomyosarcoma of omentum and mesentery; retroperitoneal leiomyosarcoma.

Intervention: Imatinib. Oral dosage -- any dose. (Where imatinib = STI 571, Glivec, Gleevec, or CGP57148).

Comparators: The ideal comparator was the current standard treatment (symptom-relief and best supportive care), or placebo. If there were no trials with

these comparators, data from trials that investigated experimental treatments in patients with GIST were sought, so that an indirect comparison could be made.

Outcomes: See the "Major Outcomes Considered" field in this summary.

Disagreements were resolved by discussion. Inclusion/exclusion decisions were made prior to detailed scrutiny of the results and study quality assessment. Foreign language publications were screened using English abstracts where available.

Stage 2 Consensus Meeting

Because the initial systematic search and sort at stage 1 had yielded in excess of 1000 papers using the above criteria, it was felt that tighter criteria were needed to eliminate papers that could not add substantial value to the review. In particular a large yield had come from prognosis/natural history papers and diagnostic papers. It was therefore agreed that the following inclusion criteria were to be applied:

Imatinib effectiveness - any patient with GIST (at any stage) who has been treated with imatinib. Ignore reviews and case studies of single patients published in abstract form only.

Other treatments -- any patient with GIST (at any stage) who has been treated with drugs other than imatinib, also include other procedures (e.g., surgery, radiotherapy, brachytherapy). Exclude papers that compare surgical laparoscopy vs. open surgery.

Prognosis -- papers describing primary research that involved the prognosis of 10 or more patients where clinical outcomes are described. Ignore reviews.

Diagnosis -- papers describing primary research that involved 10 or more patients with clinical outcomes reported. Major reviews on diagnostic accuracy or diagnostic criteria of GIST, especially those describing advanced disease were included.

Three reviewers applied the criteria on the papers selected at stage 1, and disagreements were resolved by discussion.

Stage 3

Full paper copies of studies identified in stage 2 were obtained for detailed examination. At this stage, additional papers were excluded as and when detailed study of the methods revealed that the paper did not meet the inclusion criteria. Usually this was because the wrong populations had been used; in particular some papers on examination had used patients with primary disease that was treatable with surgery and was not metastatic. Translations were also obtained on full papers where necessary or where possible. Translations were not obtained for 4 case studies included in the review, as it was not felt that a translation would add value to the review.

Data Extraction Strategy

Two reviewers independently extracted data using a pre-designed data extraction form (see Appendix 2 page 81 in the assessment report). Disagreements were resolved by discussion, consulting with a third party where necessary. Where there was missing information and time constraints allowed, the authors were contacted. Data from studies with multiple publications were reported as a single study but the source of the publications was noted.

Quality Assessment Strategy

Quality of studies was assessed using the York CRD criteria for experimental and observational studies (Appendix 11, page 128 in the assessment report). These criteria were tested and revised where necessary. The following quality issues were felt to be of paramount importance: study design, patient characteristics, (in terms of GIST diagnosis, disease severity, length of time with GIST), and any possible sources of biases in patient selection, treatment provided, and outcomes measured; where found these were reported.

NUMBER OF SOURCE DOCUMENTS

Imatinib Treatment

Two uncontrolled trials and 8 single case studies that treated cKIT positive patients with unresectable and/or metastatic gastro-intestinal stromal tumours (GIST) with imatinib were published as full papers and were included from the systematic search. The main characteristics of these studies are shown in Table 2 of the assessment report, together with information on 4 trials and one case series published in abstract form only.

Alternative Treatments

Eleven published trials and 4 single case studies were identified from the systematic review. The characteristics of these studies are shown in Table 3 of the assessment report. None of the trials prospectively tested patients for cKIT s they commenced before the test was available. A retrospective analysis of patients for cKIT was undertaken in one report.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the West Midlands Health Technology Assessment Collaboration (see the "Companion Documents" field).

Methods of Analysis/Synthesis

A descriptive analysis of each individual included study was undertaken with the relevant evidence categorised and summarised in tables. Summary tables of survival, tumour response, adverse events, and quality of life were constructed. Where appropriate, results from individual studies were quantitatively pooled by meta-analysis. Identified research evidence was interpreted according to the assessment of methodological strengths and weaknesses and the possibility of potential biases.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients, and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

No published cost-effectiveness analyses or quality-of-life studies for patients with advanced gastro-intestinal stromal tumours (GIST) were identified in the literature. The manufacturer submitted an economic model, and the Assessment Group re-analysed this model to overcome identified shortcomings. The Assessment Group also developed its own economic model, which was revised after discussion at the committee meeting to answer questions raised about some of the assumptions underpinning all the models. See Section 4.2 of the original guideline document for a detailed discussion and more information.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Imatinib treatment at 400 mg/day is recommended as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic gastro-intestinal stromal tumours (GISTs).
- Continuation with imatinib therapy is recommended only if a response to initial treatment (as defined below) is achieved within 12 weeks.
- Responders should be assessed at intervals of approximately 12 weeks thereafter. Continuation of treatment is recommended at 400 mg/day until the tumour ceases to respond, as defined below.
- An increase in the dose of imatinib is not recommended for people receiving imatinib who develop progressive disease after initially responding (see below).
- For the purpose of this guidance, response to imatinib treatment should be assessed on the basis of the results of diagnostic imaging to assess size and density of the tumour(s), patients' symptoms, and other factors, in accordance with the Southwest Oncology Group (SWOG) criteria detailed in Appendix D of the original guideline document. For the purpose of this guidance, response to therapy is defined as the SWOG classifications of complete response, partial response, or stable disease.
- The use of imatinib should be supervised by cancer specialists with experience in the management of people with unresectable and/or metastatic GISTs.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours

POTENTIAL HARMS

The most commonly reported side effects of imatinib include nausea, diarrhoea, periorbital oedema, muscle cramps, fatigue, rash, and headache. The most common serious adverse events were unspecified haemorrhage and neutropenia, each event occurring in approximately 5% of patients.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation and Audit

- All clinicians who treat people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic gastro-intestinal stromal tumour (GIST) should review their current policies and practice to take account of the guidance set out in Section 1 of the original guideline document (and the "Major Recommendations" field).
- Local guidelines or care pathways for the care of patients with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST should incorporate the guidance.
- To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C of the original guideline document.
    - For a person with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST, imatinib treatment at 400 mg/day is provided as first-line management for up to 12 weeks.
    - Imatinib therapy at 400 mg/day is continued beyond the first 12 weeks only if a person's GIST responds to treatment within 12 weeks. (Response to treatment is defined in Section 1.5 and Appendix D of the original guideline document.)
    - A person whose GIST has responded to imatinib therapy is assessed at intervals of approximately 12 weeks and imatinib therapy at 400 mg/day is continued until the GIST ceases to respond. (Response to treatment is defined in Section 1.5 and Appendix D of the original guideline document.)
    - If progressive disease develops in a person whose GIST initially responded to imatinib therapy, the dose of imatinib is not increased.
    - A cancer specialist with experience in the management of people with metastatic and/or unresectable GISTs supervises the use of imatinib.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Foreign Language Translations
Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours. London (UK): National Institute for Clinical Excellence (NICE); 2004 Oct. 38 p. (Technology appraisal; no. 86).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Oct

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. 11 Strand, London, WC2N 5HR.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2004 Oct. 2 p. (Technology appraisal 85). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Imatinib for the treatment of patients with unresectable and/or metastatic gastro-intestinal stromal tumours--a systematic review and economic evaluation. Assessment report. Birmingham (UK): West Midlands Health Technology Assessment Collaboration; 2003 Oct 10. 142 p. (Technology appraisal 85). Electronic copies: Available in PDF from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria can be found in Appendix C of the original guideline document.

PATIENT RESOURCES

The following is available:

- Imatinib for gastro-intestinal stromal tumours: understanding NICE guidance - information for adults with gastro-intestinal stromal tumours, and the public. London: National Institute for Health and Clinical Excellence. 2004 Oct. 10 p. Available in English and Welsh in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

NGC STATUS

This NGC summary was completed by ECRI on November 10, 2005.

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